

Antibiotic Resistance, Still a Global Challenge

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ABSTRACT: The use of antibiotics represents a major health problem worldwide because they are often administered without medical prescription. This has led to different situations starting from a large use in inappropriate cases without medical recommendation, to a major issue that represents antimicrobial resistance. Our aim was to identify the opinion of healthcare workers (physicians and pharmacists) about the most effective solution at reducing antimicrobial resistance, helping the policy makers to take a decision. The present study was conducted from March 15th, 2021 to April 15th, 2021, using a virtual questionnaire. A total of 397 respondents provided a complete response to our questionnaire: 313 physicians and 84 pharmacists. Our results provided valuable insights that can be used to inform the development of a national health policy, resulting in population health gains. Our work provided an indication of physicians' preferences toward solutions as "A tax on antibiotic consumption, which could be used to fund innovation strategies." (41.53%) and "An educational program for patients that highlights the causes and effects of antimicrobial resistance." (42.49%). The pharmacists preferred the solutions as "An educational program for patients that highlights the causes and effects of antimicrobial resistance." (52.38%) and "Elimination of antibiotics from the list of the emergency pharmaceutical services." (42.86%). A small number of physicians (2.24%) and pharmacists (3.57%) recommended as the most effective solution at reducing antimicrobial resistance "Restrain antibiotic use in the food industry."

KEYWORDS: Antibiotic resistance, pharmacists, physicians.

Introduction

Antibiotics are active substances, discovered almost a century ago, in 1928, by Alexander Fleming, that have action against bacteria.

These drugs have become indispensable in current medical practice and even in various industries, such as the food industry or in agriculture [1].

Antibiotics saved countless lives and are used by practitioners nowadays to treat bacterial infections.

Although there are guidelines that recommend the use of antibiotics in various conditions, in countries where the economy or the public healthcare system and education are underdeveloped, these substances are used irrationally [2].

The use of antibiotics in an unjustified manner has become a real public health problem worldwide, uncontrolled usage of this type of medicine has led to antimicrobial resistance (AMR) [3].

AMR is known to be one of the most dangerous threats of the global health system. CDC reports more than 2.8 million antimicrobial-resistant infections in the U.S.

each year, and more than 35,000 deaths as a result [4].

European Antimicrobial Surveillance Network reports from 2019 show that each year, approximately 33000 people die as a direct consequence of AMR in EU and EEA countries [5].

AMR leads to multiple complications in the background of the main illness, ineffectiveness of different medication or the prolonged hospitalization period [6.]

It is important to understand what has misdirected to this state of the healthcare system itself, like the denial of patients to be treated in a correct manner by the practitioners, or their lack of interest regarding their status and refusing the treatment, or even the unjustified over-the-counter usage of different pharmaceutical substances [7].

Amenable for action towards the screening of AMR are both individual and institutional parties: practitioners who prescribe drugs without following strict guidelines or without adequate diagnosis, the pharmaceutical industry which promotes antimicrobial products, food and veterinary industries, the lack of public health education among

antibiotic consumers and cultural or political malfunctions [8,9].

Our aim was to identify the opinion of healthcare workers (physicians and pharmacists) about the most effective solution at reducing antimicrobial resistance, helping the policy makers to take a decision.

Material and Methods

The present study was conducted from March 15th, 2021 to April 15th, 2021, using a virtual questionnaire.

The questionnaire was developed using Google Forms and had two parts: the socio-demographic characteristics and the perception towards the most effective solution for reducing antimicrobial resistance.

The online survey was anonymous and confidential, we obtained the participants' informed consent from the first statement of the survey.

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the University of Medicine and Pharmacy of Craiova (Registration no. 88/2020).

In the first phase, the items were generated based on an ample literature review related to solutions proposed to resolve the AMR issue.

Some well-known solutions implemented in health policies were included in our questionnaire: "An educational program for patients that highlights the causes and effects of antimicrobial resistance", "A program for physicians that focuses not on the immediate benefit of the treatment to their patients, but the effect it may have on the community and the emergence of AMR." and "Restrain antibiotic use in the food industry".

One of the solutions was proposed following the experience as pharmacist working in a community pharmacy from Romania: "Elimination of antibiotics from the list of the emergency pharmaceutical services".

Antibiotics are prescription drugs in Romania, they legally require a medical

prescription to be dispensed in a community pharmacy.

But, in an emergency pharmaceutical service, the pharmacist may dispense antibiotics without a prescription for 24 hours or 3 days in weekends or legal holidays.

As psychotropic and narcotic drugs are not subject to emergency pharmaceutical services, in the same way, antibiotics must not be subject to emergency pharmaceutical services and they must require a medical prescription to be dispersed all the time.

A new solution was proposed by *Giubilini et al.* [10] who suggested taxing certain use of antibiotics, as in minor and self-limiting infections treatment, drawing an analogy with taxing on consumption of alcohol and tobacco, which also causes negative externalities.

The tax on antibiotics dispersing was considered effective at reducing antibiotics consumption since level of consumption is sensitive to price.

Furthermore, the tax on antibiotics could be collected to fund innovation strategies.

We also took into account information on whom would recommend more antibiotics were did the medical personnel gets their information on antibiotic usage.

Data were analysed using GraphPad Prism 9.1.0 (GraphPad Software, San Diego, CA, USA).

The Mann-Whitney and χ^2 test was used to compare demographical characteristics and responses of the healthcare workers.

The $\alpha < 0.05$ level was considered for statistical significance.

Results

A total of 397 medical care providers helped helped with a complete response to our questionnaire: 313 physicians and 84 pharmacists.

The sample included a larger proportion of women (67.26%), the mean age (SD) was 36.45 (10.40).

The pharmacists were younger, with more women and less specialists than physicians. (Table 1)

Table 1. The socio-demographic characteristics of the respondents.

Characteristics	Respondents (n=397)		p-value
	Physicians (n=313)	Pharmacists (n=84)	
Age, years (mean±SD)	37.88±10.68	31.13±7.08	<0.0001
≤30 (n, %)	90 (26%)	57 (68%)	
31-40	120 (35%)	19 (23%)	
41-50	53 (15%)	6 (7%)	
51-60	37(11%)	2 (2%)	
>60	13 (4%)	0	
Gender (n, %)			<0.0001
Male	123 (39%)	9 (11%)	
Female	190 (61%)	75 (89%)	
Speciality			<0.0001
Fellows	106 (34%)	72 (87%)	
Specialist	103 (33%)	7 (8%)	
Senior specialist	104 (33%)	5 (5%)	

Table 2. Medical care workers perspective on antibiotic perscription.

	Physicians	Pharmacists	All
Patients	114 (36,42%)	32 (38,09%)	146 (36,77%)
Specialists	68 (21,73%)	18 (21,42%)	86 (21,66%)
Pharmacists	35 (11,18%)	11 (13,09%)	46 (11,58%)
Family medicine doctors	96 (30,67%)	23 (27,38%)	119 (29,97%)

On the other hand, we tried to see what was the medical care opinion on whom might be acquainted of antibiotic prescription.

The survey revealed that that both the physicians and the pharmacist suggest that the patients are more proned to ask for antibiotics (36,77%), followed by the family doctors prescriptions (29,97%), specialists (21,66%), and pharmacists (11,58%). (Table 2)

We also assessed why physicians are more likely to prescribe antibiotics without a firm indication and pointed out that most of the physicians felt that “even though they were not the infection was caused by a virus or bacteria” ambulatory patients should receive antibiotics (33,4%), followed by “loss of follow-up, or the fact they were not able to follow-up patients” (20,5%).

However, most of the physicians concluded that they would only prescribe antibiotics when indicated (46,1%).

We also tried to compare how physicians and pharmacists on their knowledge on AMR. As expected, physicians (94,2%) were more assertive on antibiograms interpretations than pharmacists (68,5%).

Even more, when taking into account infections, physicians were better prepared in chosing proper sources for infection treatment and antibiotic guideline usage than the pharmacists.

When discussing medical sources of information, most of the physicians and

pharmacist seem to chose the proper way to inform them selves with guidelines (90,41% vs. 44,04%), medical journal and textbooks (82,62% vs. 27,38%), as well as congresses (87,85% vs. 17,85%) being the top choices.

However a considerable number also choosed the Google search (50,79% vs. 20,23%) as a tool to search about information on antibiotics prescriptions. (Table 3)

Our results provided valuable insights that can be used to inform the development of a national health policy, resulting in population health gains. Some differences of choices were observed between the physicians and pharmacists.

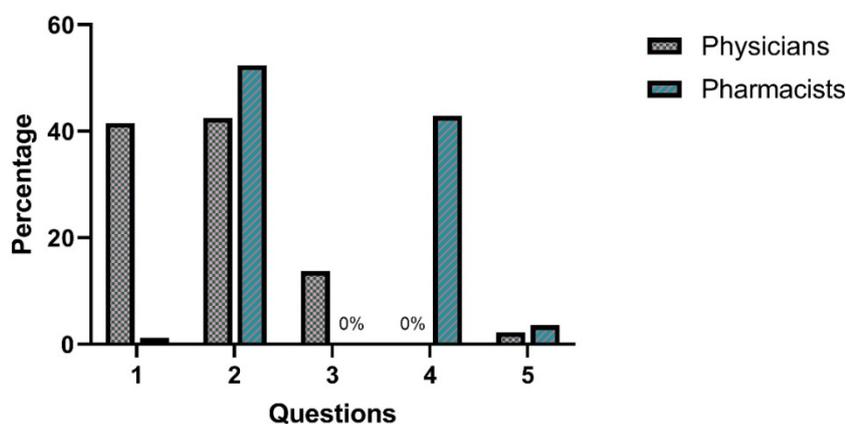
Our work showed an indication of physicians' preferences towards solutions as “A tax on antibiotic consumption, which could be used to fund innovation strategies.” (41.53%) and “An educational program for patients that highlights the causes and effects of antimicrobial resistance.” (42.49%).

The pharmacists preferred the solutions as “An educational program for patients that highlights the causes and effects of antimicrobial resistance.” (52.38%) and “Elimination of antibiotics from the list of the emergency pharmaceutical services.” (42.86%).

A small number of physicians (2.24%) and pharmacists (3.57%) recommended as the most effective solution at reducing antimicrobial resistance Restrain antibiotic use in the food industry.” Figure 1

Table 3. Physicians and pharmacists source of information.

	Physicians (313)	Pharmacists (84)
Guidelines	283 (90,41%)	37 (44,04%)
Textbooks and Medical Journals	268 (85,62%)	23 (27,38%)
Smart Phone apps	116 (37,06%)	21 (25%)
Congresses	275 (87,85%)	15 (17,85%)
Google search	159 (50,79%)	17 (20,23%)



1. A tax on antibiotic consumption, which could be used to fund innovation strategies.
2. An educational program for patients that highlights the causes and effects of antimicrobial resistance.
3. A program for physicians that focuses not on the immediate benefit of the treatment to their patients, but on the effect it may have on the community and the emergence of AMR
4. Elimination of antibiotics from the list of the emergency pharmaceutical services.
5. Restrain antibiotic use in the food industry.

Figure 1. The responses of the healthcare workers (physicians and pharmacists).

The idea that an antibiotic tax would be effective at reducing antibiotic consumption was preferred more by the physicians than by pharmacists.

An willingness to pay for antibiotics tax and how this tax will change its consumption frequency for antibiotics must be done in future studies, among different scenarios and targeted patients.

Both physicians and pharmacists are aware of the importance of an educational program for patients that focus attention on the consequences of AMR.

Knowing patients' attitudes in the community pharmacy, the pharmacists elected the solution of eliminating the antibiotics from the list of the emergency pharmaceutical services, thus eliminating any possibility of antibiotics dispensing without prescription.

The pharmacists have a high degree of confidence in the doctors' decision on antibiotics prescribing, none of them considered as being the most effective solution a program for physicians.

Discussions

It is mandatory to promote innovation and interest in innovative research, since the trend is continuously ascending regarding antimicrobial resistance.

In Europe, in the last four years, in countries like Norway and Estonia, statistics show a decrease regarding resistant strains of *Acinetobacter* or *Klebsiella Pneumoniae*, but for the most EU member states, for *Klebsiella Pneumoniae*, *Escherichia Coli* with resistance to third generation cephalosporins, the European Centre for Disease Prevention and Control reports an expansive line regarding the presence of resistant bacteria [11].

Ethical problems which may appear in the process of prescribing antibiotics sum up the idea of protecting the patients and also of the available powerful medication.

Healthcare providers should have certain guidelines, tailored to their working and policy regulations, thus allowing them to provide the most beneficial treatment.

Pathogen’s transmission is made in multiple paths, through physical transmission, respiratory spreading or ingestion [12].

By touching infected surfaces, the transfer or microorganisms is made and the spread of bacteria is assured.

Especially in hospitals, where compromised patients are more prone to be harmed and the costs of a prolonged hospitalization and treatment, detection, investigation and control of infectious conditions, as well as preventive measures should be implemented: hygiene, screening and diagnosis, isolation and correct ventilation [13].

Regarding the topic, AMR is the main focus of multiple domains which have a symbiosis connection as a whole.

Governing principles may cause eminent outbreaks between both the healthcare system and pharmacy industry.

Imagine the consequences of an industry which would threaten to increase the costs of antibacterial drugs to finance the research of future medication [14].

This would force the economy to commercialize unnecessary antibiotics in order to regain the stability of the market, and therefore, the antimicrobial resistance would increase progressively.

Public awareness campaigns should be a leading strategy for the governing parties, while education is a key point of the evolution of every society (Table 4).

Empiric ant biotherapy should be approached through perspectives emphasizing the real need of antibiotic use, and such treatment would only be given to patients suffering of bacterial infections.

In patients with severely altered life condition or terminal ill dementia, the result of antibiotic use is irrelevant, while the use of broad spectrum empirical antibiotic medication is cost-benefit ineffective.

Repetitive treatment with broad-spectrum drugs leads in a short amount of time to infections initiated by resistant pathogens [15].

Our results raise some questions on the available perception of the medical personnel on how antibiotics should be prescribed and their indication.

A rather debatable situations is the use of Google search for acquiring information, which might actually happen because it is an easy to access tools for everybody.

However, both the pharmacists and the physicians still focus on guidelines, textbooks and highly impact resources provided from medical congresses.

Governing misinterpretation while evaluating antimicrobial resistance

In low-income countries, where economic evaluation is insufficient, the misinterpretation of AMR incidence is dangerous in evaluating the real picture of it.

Even in high-income countries, where there are multiple economic statistics, the state of the AMR burden is also underestimated.

Not accounting the repercussions and the cost associated effects of the pathogens resistance, the misuse of antibiotics, imperfect public health education and medical services will conduct to a dangerous and unskilled era in which the next generation will have to face the future problems of a higher severity [16].

In the idea of spreading resistant pathogens, an important role is played by the environment and industrial factors which also need to evolve in order to satisfy the requirements and demands of world population.

Wastewater is a hotspot for gene transfer [17] and strategies that are made to reduce and neutralize the manmade AMR play a key role in the effort towards control and counterattack [18].

Table 4. Possible strategies to reduce and neutralize AMR.

Medical Staff	Patients	Government	Pharmaceutical Industry
Respect guidelines	Follow prescriptions	Organize educational programs	Collaboration premises
Investigate patients disease properly	Consult the healthcare provider	Strict regulations of the access	Technical innovation
Offer data if required	Develop positive attitude to education	Clinical trial networks for infections which are difficult to treat	
Promote medical education	Infection prevention through prophylaxis	Restrain antibiotic use in the food industry	

Conclusion

AMR is a problematic global health concern worldwide, rising manifold questions regarding managing skills of the governments.

Options are needed, as well as a way to balance not only scientific innovation, but also desperate necessity for a proper treatment.

Current approaches of this theme are overwhelmed by the capacity of a single microorganism to evolve and to subjugate the efforts of public healthcare teams.

Commitment from pharmaceutical industry, public regulations and local manufacturers, sharing both resources and risk assessed information, on a global scale, would ensure positive progress.

There is clear evidence that antibiotics are not commercially attractive, compared to chronic illness, in which a patient requires a prolonged treatment, or even viral drugs and vaccines.

Options are required, and an effective basis would help balancing all needs, medical staff, patients, government and pharmaceutical industry.

References

1. Capita R, Alonso-Calleja C. Antibiotic-Resistant Bacteria: A Challenge for the Food Industry. *Crit Rev Food Sci Nutr*, 2013, 53(1):11-48.
2. Merrett GLB, Bloom G, Wilkinson A, MacGregor H. Towards the just and sustainable use of antibiotics. *J Pharm Policy Pract*, 2016, 7(9):31.
3. Van Boeckel TP, Gandra S, Ashok A, Caudron Q, Grenfell BT, Levin SA, Laxminarayan R et al. Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. *Lancet Infect Dis*, 2014, 14(8):742-750.
4. Centers for Disease Control and Prevention, 2019. ANTIBIOTIC RESISTANCE THREATS IN THE UNITED STATES [online]. Available at: <https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf>.
5. World Health Organization, 2015 Global Action Plan on Antimicrobial Resistance [online]. Available at: https://apps.who.int/iris/bitstream/handle/10665/193736/9789241509763_eng.%0Apdf?sequence=1.
6. World Health Organization, 2014. Antimicrobial Resistance: Global Report on Surveillance [online] Available at <https://apps.who.int/iris/handle/10665/112642>
7. Bagnulo A, Sastre MTM, Kpanake L, Sorum PC, Mullet E. Why patients want to take or refuse to take antibiotics: An inventory of motives. *BMC Public Health*, 2019, 19(1):1-9.
8. Heyman G, Cars O, Bejarano MT, Peterson S. Access, excess, and ethics-towards a sustainable distribution model for antibiotics. *Ups J Med Sci*, 2014, 119(2):134-141.
9. Parsonage B, Hagglund PK, Keogh L, Wheelhouse N, Brown RE, Dancer SJ. Control of antimicrobial resistance requires an ethical approach. *Front Microbiol*, 2017, 8(NOV):1-14.
10. Giubilini, A. Antibiotic resistance as a tragedy of the commons: An ethical argument for a tax on antibiotic use in humans. *Bioethics*, 2019, 33: 776-784.
11. European Centre for Disease Prevention and Control, 2018. Surveillance of Antimicrobial Resistance in Europe [online] Available at: <https://ecdc.europa.eu/en/publications-data/antimicrobial-resistance-surveillance-europe-2016>.
12. Morehead MS, Scarbrough C. Emergence of Global Antibiotic Resistance. *Prim Care-Clin Off Pract*, 2018, 45(3):467-484.
13. Burke JP. Infection control-A problem for patient safety. *N Engl J Med*. 2003;348(7):651-656.
14. European Commission, 2017. A European One Health Action Plan against Antimicrobial Resistance (AMR) [online]. Available at: https://ec.europa.eu/health/amr/sites/amr/files/%0Aamr_action_plan_2017_en.pdf. Published 2017.
15. Leibovici L, Paul M. Ethical dilemmas in antibiotic treatment: Focus on the elderly. *Clin Microbiol Infect*, 2015, 21(1):27-29.
16. Fair RJ TY. Antibiotics and bacterial resistance in the 21st century. *Perspect Medicin Chem*, 2014, (6):25-64.
17. Laxminarayan R, Duse A, Wattal C, Zaidi AKM, Wertheim HFL, Sumpradit N, Vlieghe E, Hara GL, Gould IM, Goossens H, Greko C, So AD, Bigdeli M, Tomson G, Woodhouse W, Ombaka E, Peralta AO, Qamar FN, Mir F, Kariuki S, Bhutta ZA, Coates A, Bergstrom R, Wright GD, Brown ED, Cars O Antibiotic resistance-the need for global solutions. *Lancet Infect Dis*, 2013, 13(12):1057-1098.
18. Verheij TJ. The antibiotic revolution should be more focused. *BrJGen Pr*, 2009, 59(567):716-717.

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